Standard Operating Procedure for the Preparation of a Trial Specific Randomisation, Blinding and Code Break Standard Operating Procedure

SOP ID Number : JRO/INV/S06/05	**Effective Date:** 12/03/21
Version Number & Date of Authorisation: V05, 12/02/21	**Review Date:** 12/03/24
SOP eDocument kept : S:_SLMS\RSC_ALL_STAFF\CLINICAL_TRIALS\SOPs\EFFECTIVE_SOPs_Guides\Investigator SOP\INV_S06 preparation for randomisation, blinding and code breaks\INV_S06_SOP Preparation for Randomisation_Unblinding_Code Break_V05_12.03.21.doc	

Revision Chronology:			
SOP ID Number:	**Effective Date:**	**Reason for Change:**	**Author:**
JBRU/INV/S06/01	28/12/09	NA	Anne Marie Downey
JRO/INV/S06/02	11/01/12	Due for review. No changes beside JBRU replaced by JRO	Anne Marie Downey
JRO/INV/S06/03	12/01/15	Due for Review. Changes to update the content in the SOP	Nimrita Verma
JRO/INV/S06/04	16/01/18	Due for Review. Changes to update the content in the SOP	Nimrita Verma
JRO/INV/S06/05	12/03/21	Due for Review. - Updated definition for interactive voice/web system and used the more commonly used term IxRS to include both IVRS and IWRS. - Added use of the Code Break (Unblinding) Log for documenting code breaks on the trial. - Added prompt to test the code break / emergency contact telephone number & use of Testing Log template	Samim Patel

ACRONYMS:	
CI	Chief Investigator
CRF	Case Report Form
DSMC	Data Safety Monitoring Committee
GCP	Good Clinical Practice
IxRS	Interactive Voice / Web Response System
JRO	Joint Research Office UCLH/ UCL
SOP	Standard Operating Procedure

DEFINITIONS

Allocation concealment: Is where the person randomising the patient does not know what the next treatment allocation will be.

Blinding: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s).

Block Randomisation: Is the arranging of treatment allocations in groups (blocks) that are similar to one another.

Code Break: is also known as breaking the blind. It is the mechanism that permits the rapid identification of the trial treatment in case of a medical emergency, but does not permit undetectable breaks of the blinding.

Double-blinding: Where the subject(s), Investigators, monitor and in some cases, data analyst(s) are unaware of the treatment assignment(s).

Interactive Voice / Web Response System (IxRS): An Interactive Response System, which can be accessed via telephone or web. It can be configured and customised to allow trial teams to manage key aspects of their clinical trials including enrolment/randomisation, dosing/drug dispensing, clinical supplies, drug inventory management and unblinding.

Randomisation: The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Randomisation Code: A unique number or code that is linked via a randomisation list to the treatment.

Simple Randomisation: is a subset of individuals (a sample) chosen from a larger set (a population). Each individual is chosen randomly with equal chance of receiving each treatment.

Single-Blind: Where the subject(s) are unaware of the treatment assignment(s).

Stratification: A sampling procedure in which the population is divided into homogeneous subgroups or strata and the selection of samples is done independently in each stratum.

Un-blinding: Is the disclosure of the identity of blinded treatment.

Standard Operating Procedure for the Preparation of a Trial Specific Randomisation, Blinding and Code Break Standard Operating Procedure

1. PURPOSE

This Standard Operating Procedure (SOP) has been written by the JRO to describe the procedure that the CI must follow for the Preparation of a **trial Specific** Randomisation, Blinding and Code Break Standard Operating Procedure.

2. JOINT UCLH/ UCL RESEARCH OFFICE POLICY

All JRO SOPS are produced, reviewed and approved in accordance with the JRO SOP on SOPs.

3. BACKGROUND

All SOPs are written in accordance with applicable GCP requirements as outlined in Directives 2001/20/EC and 2005/20/EC (these Directives were transposed into UK law by SI 2004/1031, SI 2006/1928) and subsequent amendments. Where applicable, it incorporates elements of ICH GCP tripartite guidelines (E6).

In addition, for trials with EU and Northern Ireland site the SOPs will have to be compliant with EU Clinical Trials Regulation No. 536/2014 if/when applicable.

Clinical trials are often blinded to hide the treatment group assignment from participants and/ or Investigators in order to prevent the unintentional biases of either party affecting subject data.

Clinical trials comparing one or more treatments or placebo may be randomised such that participant treatment allocation occurs at random.

In order to protect the wellbeing and safety of the trial subject as required in the principles of GCP, the coding system for the Investigational Medical Product(s) in blinded trials should include a mechanism that permits rapid identification of the Investigational Medicinal Product(s) in case of a medical emergency, but one that does not permit undetectable breaks of the blinding in order to protect the integrity and validity of the data. To ensure this, code break procedures must be clearly established.

At the start of any clinical trial the CI should have a written procedure for the randomisation, blinding and process for rapidly identifying a blinded Investigational Medicinal Product(s), as well as the details of authorised personnel who will have access to un-blinded data.

4. SCOPE OF THIS SOP

The scope of this SOP is to describe the procedure for the CI to write a trial specific Standard Operating Procedure on Randomisation, Unblinding and Code Break procedures (as applicable) for all randomised controlled clinical trials sponsored by UCL and managed by the JRO.

The Trial Specific SOP should be drafted using the JRO **Trial Specific SOP for Randomisation, Unblinding and Code Break** template. The SOP should be written in conjunction with setting up the randomisation process and drafting of the protocol in accordance with the JRO Protocol template.

It is strongly recommended that for double-blind, randomised controlled trials, the Chief Investigator considers using an external supplier that provides an interactive voice/web response system (IxRS) for randomisation, blinding and code breaks.

5. RESPONSIBLE PERSONNEL

Any researcher or member of a study team who has been given the responsibility for writing the trial specific SOP for Randomisation, Unblinding and Code Break in a clinical trial should follow this SOP.
The CI of the trial must review, correct as necessary, sign and date the Trial Specific SOP. The Trial Specific SOP must also be reviewed by a representative of the Sponsor.

The CI is responsible for training all staff personnel in the trial team to ensure the Trial Specific SOP for Randomisation, Unblinding and Code Break is well understood and complied with.

In multicentre trials the CI is responsible for ensuring all PIs and trial teams at participating sites are trained and familiar with the Trial Specific SOP for Randomisation, Unblinding and Code Break.

6. PROCEDURE

6.1 Randomisation Procedure

The CI needs to determine what type of method will be used to reduce the chance of imbalance between treatment groups. The design and type (simple, block, stratified, minimisation) should be detailed in the protocol and in the SOP.
The CI must consult with a qualified statistician (JRO or external) to determine the type of randomisation needed and refer to the JRO's SOP for producing randomisation lists for trials. (JRO/SPON/S05)

Once the design and type of randomisation has been established in the protocol, a randomisation list with details of the randomisation codes should be produced in accordance with the protocol. The list should be generated by a person who has no direct contact with the trial subjects or involvement with the assessment for eligibility in the trial. It is recommended that the CI considers using an external source to perform this task using an IxRS.

In cases of trials that are single site involving small numbers, and depending on the complexity of the randomisation required, a qualified statistician or data manager may perform this task.

The process used to produce the randomisation list and how randomisation will be implemented should be documented in the Trial Specific SOP with the following considerations made:

- A brief description of the randomisation process
- Variables used in the procedure to be recorded
- The name and job title of the person generating the randomisation list
- Computer software that will be used to generate the list and perform randomisation (if applicable) and details on the validation of this system before it is used.
- What approach will be used to conceal allocation (e.g. password protected electronic format), and details on location of the randomisation list and how it will be stored securely.
- For small noncomplex single site trials a system of sealed envelopes may be used. The CI must ensure that all seals of these envelopes are signed and dated and that the CI collects the envelopes at the end of the trial to ensure that the seals have not been broken.
- The name and job title of the person who will have access to the randomisation list and will be responsible for randomisation (NB: for double blinded trials the randomisation list should not be made available to the CI and their trial team until database lock and the codes have been officially broken at the end of the trial).
- For blinded trials, the CI will need to provide details on how the randomisation codes will be provided to the IMP manufacturer to ensure the IMP are packaged, coded and labelled in a manner that protects the blinding.
- Details on the randomisation process including telephone numbers and or web links, the open times for randomisation and procedure to be used out of hours if applicable (e.g. randomisation hours between 0900hr-1700hr, Monday to Friday).
- Details of the documentation to be completed for randomisation (e.g. signed informed consent form, randomisation checklist/ CRF or eligibility criteria checklist CRF)
- Details on how pharmacy will be informed of the randomisation treatment code allocation (e.g. email sent to pharmacy).
- Should include the provision of a trial specific patient card with contact details (including out of hours contact details) for emergencies.

6.2 Blinding

The protocol and SOP should define the level of blinding (e.g. nblended, single-blind or double-blind) and how the blinding will be implemented (e.g. through the use of an identical placebo).

For double blinded trials the SOP should include the following:

- How the IMP will be packaged, coded and labelled in a manner that protects the blinding (NB: labelling should not make reference to group allocation). Refer to Sponsor's SOP on IMP labelling (JRO/SPON/S09).
- The statement 'The blinding of the trial must be maintained throughout the trial until all data entry and processing are complete and the database has been locked.'

6.3 Code Breaking (Unblinding)

The code break process should be detailed in the protocol and the procedure thoroughly documented in the trial specific SOP and needs to include the following considerations:

- **Circumstances** where unblinding of the individual can be undertaken such as:

  - In a medical emergency where knowledge of the blinded treatment is necessary, for the treatment of an adverse event,

  - Where a child in a participant's household accidentally takes an IMP,

  - In the event of a SUSAR (Suspected Unexpected Serious Adverse Reaction) needing expedited reporting,

  If requested by a Data Safety Monitoring Committee (DSMC).

- Details on the **format** of the code break (i.e. 24 hour telephone number, scratch cards, tear off labels, IxRS).
- How the code break information will be made available to all healthcare professionals i.e. by use of a 24 hour contact card (24 Hour contact card template is available with this SOP).
- How the code break information will be made available to the Sponsor for the purposes of reporting SUSARs to the MHRA and REC i.e. by providing JRO representatives unblinding access to the IxRS.
- Where sealed code break envelopes are used, the envelopes are to be signed on both seals, and in the event of a code break the name of the code breaker, the signature, date and time needs to be recorded on the outside of the envelope.
- Specify the storage location of the code break envelopes which should only be accessible by the un-blinded site staff.
- If code break envelopes are used, the SOP should give details on the collection of envelopes by the CI at the end of the trial and provide information on where the code break envelopes will be held during the trial.
- It is essential that, in the case of an emergency, there is a system in place for providing 24 hour cover to access the code break. It is recommended that the CI uses an IxRS. The SOP needs to provide the step by step instructions on how to code break in an emergency.
- Where code break is not fully automated at least two members of the trial team should be responsible for code break procedures.

- How the code break process will be tested (including out of hours) for example, by periodically (e.g. at least once a year) calling the 24 hour contact phone number to check that it is correct and working. Documentation of the testing should be recorded on the **Emergency Contact/Unblinding Testing Log** (see associated template).

- Specify what needs to be documented and how for any emergency code break. The SOP should request this to be documented fully on the trial specific **Code Break (Unblinding) Log** (see associated template) and should contain: The patient's trial ID, the reason for unblinding, the date of unblinding, the name of the person requesting the code break, the name of the person breaking the code and the date the Sponsor informed of the code break. In multi-site trials the CI should also be informed of the code break at the site. Any additional information on the code break can be documented on a file note.

- Detail where the **Code Break (Unblinding) Log** and additional written documentation of the code break if applicable should be filed (i.e. in the Investigator Site File).

- For single site trials, **the SOP needs to state** that the Investigator will notify the Sponsor in writing following a code break, detailing the reasons for unblinding.

- For multicentre trials, **the SOP needs to state** that the CI must inform the Sponsor and other Investigators in writing following a code break, with the reasons for unblinding.

- Provide details on circumstances where patients will be able to remain on the trial following unblinding.

- Provide details of unblinding after trial completion, i.e. when all data has been collected and all data queries have been resolved and the database has been locked, including the role of the DSMC and Statistician.

- Consider the method of informing participants of their blinded treatment allocation, if applicable.

6.4 Trial Specific SOP Dissemination and Training

All members of the trial team must be trained in the Trial Specific SOP prior to commencing work on the trial. The CI/PI should document the SOP training for each member of the research team on the SOP training log which is located at the end of the trial specific SOP.

7. REFERENCES

Directive 2001/20/EC of the European Parliament and of the Council of 4th April 2001 on the approximation of the laws, regulations and the administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031)**,** implemented on the 1st May 2004 and as amended (SI 2006/1928);

European Commission, The rules governing medicinal products in the European Union, VOLUME 4, Good manufacturing practices, ANNEX 13, Manufacture of investigational medicinal products, Revision 1, July 2003;

Sponsor's Standard Operating Procedure for the Preparation, Review and Approval of Standard Operating Procedures for UCL Sponsored Trials (JRO/SPON/S01);

Sponsor Standard Operating Procedure
For IMP Labelling (JRO/SPON/S09);

UCL CTIMPs protocol template;

Sponsor Standard Operating procedure for producing randomisation lists for trials (JRO/SPON/S05).

8. APPENDICES

Not Applicable

9. TEMPLATES/LOGS ASSOCIATED TO THIS SOP:

1	Trial specific SOP for Randomisation, Unblinding and Code Break template
2	Code Break (Unblinding) Log
3	24 Hour Contact Card template
4	Emergency Contact / Unblinding Testing Log

10. SOP DISSEMINATION & TRAINING

This SOP will be provided to the CI at the time they are drafting their protocol and their trial specific SOP on randomisation, blinding and unblinding. All trial team staff concerned by this SOP will sign the SOP training log (12. SOP TRAINING LOG) part of this SOP.

11. SIGNATURE PAGE

Author and Job Title:	Samim Patel, Sponsor Regulatory Advisor
Signature:	Samim Patel
Date:	12/02/2021

Authorised by: **Name and Job Title**	Helen Cadiou, Head of Quality Assurance
Signature:	Helen Cadiou
Date:	12/02/2021

12. SOP TRAINING LOG:

	Name of Staff (Capital letters)**:**	**Job Title:** **Department:**	**Training Date**	**I confirm that I understand & agree to work to this SOP SIGNATURE**	**Name of Trainer** (if applicable)	**Signature**	**Date**
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